JNS

CLINICAL ARTICLE

Technical and operative factors affecting magnetic resonance imaging–guided focused ultrasound thalamotomy for essential tremor: experience from 250 treatments

Myung Ji Kim, MD,[1] So Hee Park, MD,[1] Kyung Won Chang, MD,[1] Yuhee Kim, MSc,[2] Jing Gao, PhD,[2] Maya Kovalevsky, MSc,[2] Itay Rachmilevitch, BSc,[2] Eyal Zadicario, PhD,[2] Won Seok Chang, MD, PhD,[1] Hyun Ho Jung, MD, PhD,[1] and Jin Woo Chang, MD, PhD[1]

[1]Department of Neurosurgery, Brain Research Institute, Yonsei University College of Medicine, Seoul, Republic of Korea; and [2]InSightec Ltd., Tirat Carmel, Israel

OBJECTIVE Magnetic resonance imaging–guided focused ultrasound (MRgFUS) provides real-time monitoring of patients to assess tremor control and document any adverse effects. MRgFUS of the ventral intermediate nucleus (VIM) of the thalamus has become an effective treatment option for medically intractable essential tremor (ET). The aim of this study was to analyze the correlations of clinical and technical parameters with 12-month outcomes after unilateral MRgFUS thalamotomy for ET to help guide future clinical treatments.

METHODS From October 2013 to January 2019, data on unilateral MRgFUS thalamotomy from the original pivotal study and continued-access studies from three different geographic regions were collected. Authors of the present study retrospectively reviewed those data and evaluated the efficacy of the procedure on the basis of improvement in the Clinical Rating Scale for Tremor (CRST) subscore at 1 year posttreatment. Safety was based on the rates of moderate and severe thalamotomy-related adverse events. Treatment outcomes in relation to various patient- and sonication-related parameters were analyzed in a large cohort of patients with ET.

RESULTS In total, 250 patients were included in the present analysis. Improvement was sustained throughout the 12-month follow-up period, and 184 (73.6%) of 250 patients had minimal or no disability due to tremor (CRST subscore < 10) at the 12-month follow-up. Younger age and higher focal temperature (Tmax) correlated with tremor improvement in the multivariate analysis (OR 0.948, $p = 0.013$; OR 1.188, $p = 0.025$; respectively). However, no single statistically significant factor correlated with Tmax in the multivariate analysis. The cutoff value of Tmax in predicting a CRST subscore < 10 was 55.8°C. Skull density ratio (SDR) was positively correlated with heating efficiency ($\beta = 0.005$, $p < 0.001$), but no significant relationship with tremor improvement was observed. In the low-temperature group, 1–3 repetitions to the right target with $52°C \le \text{Tmax} \le 54°C$ was sufficient to generate sustained tremor suppression within the investigated follow-up period. The high-temperature group had a higher rate of balance disturbances than the low-temperature group ($p = 0.04$).

CONCLUSIONS The authors analyzed the data of 250 patients with the aim of improving practices for patient screening and determining treatment endpoints. These results may improve the safety, efficacy, and efficiency of MRgFUS thalamotomy for ET.

https://thejns.org/doi/abs/10.3171/2020.11.JNS202580

KEYWORDS essential tremor; magnetic resonance imaging–guided focused ultrasound; MRgFUS; skull density ratio; SDR; thalamotomy; functional neurosurgery

Essential tremor (ET) is the most common movement disorder, with a prevalence of up to 4% in the general population, and is characterized by a postural and intentional tremor, which can vary from a mild to a disabling high-amplitude tremor.[1] Although ET does not cause severe medical morbidity or death, it causes psychological and social disabilities and limits the activities of daily living as it progresses over time. Pharmacotherapy is the first-line treatment, but approximately 50% of people with ET develop recurrent tremor, have inadequate tremor

---

ABBREVIATIONS CRST = Clinical Rating Scale for Tremor; ET = essential tremor; MRgFUS = magnetic resonance imaging–guided focused ultrasound; SDR = skull density ratio; T-AE = thalamotomy-related adverse event; Tmax = focal temperature; VIM = ventral intermediate nucleus.

SUBMITTED July 2, 2020. **ACCEPTED** November 9, 2020.
INCLUDE WHEN CITING Published online May 21, 2021; DOI: 10.3171/2020.11.JNS202580.

control using medication, and experience medication-induced side effects.[2] A subset of these patients may consider surgical treatments such as deep brain stimulation[3] and Gamma Knife radiosurgery.[4] Magnetic resonance imaging–guided focused ultrasound (MRgFUS) thalamotomy of the ventral intermediate nucleus (VIM) of the thalamus has recently been shown to be an effective treatment option for medication-refractory ET.[5–8] MRgFUS combines the technical advantages of both MRI and a multielement FUS array and enables accurate and spatially controlled energy deposition deep within the brain in a completely noninvasive manner. It facilitates real-time monitoring of patients to evaluate the degree of tremor control while identifying any possible adverse effects and providing essential diagnostic imaging information. Based on experience, clinical testing paired with intraoperative imaging as well as an empirical knowledge on operative parameters can help physicians decide whether sufficient lesioning has been accomplished for effective and durable tremor suppression. This study provides practical information regarding the direct effect of operative variables on clinical outcomes on the basis of an analysis of data from 250 MRgFUS thalamotomies. These findings may help with future patient selection strategies, personalized treatments, and improvement in the efficacy and safety of treatments.

Methods

Patients

From October 2013 to January 2019, 260 patients with medication-refractory ET underwent unilateral MRgFUS thalamotomy at 22 medical centers worldwide. Among these patients were 56 who were actively treated in a randomized, sham-controlled, pivotal study and 21 (19 patients in the sham group and 2 patients with technical failure in the treatment group) who were switched to active treatment after 3 months. The other 183 patients were recruited into a single-arm, continued-access study conducted in the United States, Europe, and Asia. Patients were recruited on the basis of previously described eligibility criteria.[5] Since 2014, patients have been screened according to their skull density ratio (SDR) on computed tomography (CT). All patients provided written informed consent before the study began, and this study received full ethics approval from the institutional review board of each participating center.

MRgFUS Thalamotomy

Details of the MRgFUS thalamotomy procedure have been described previously.[5,8] Briefly, all procedures were performed using a 1.5-T or 3-T MRI system (GE Medical Systems) with an ExAblate Neuro 4000 device (InSightec Ltd.). Each patient's head was fixed in a Radionics frame (Integra Radionics). After refinement between the transducer focus and the target with low-dose, sublethal energy sonications, unilateral lesioning was performed with a series of ablative sonications. During the delivery of acoustic energy, temperature elevation was monitored using real-time MR thermometry, and each patient was assessed for tremor improvement and adverse events. Clinicians could decide to move the target from the first lesion or to repeat sonications on the basis of the tremor response.

Outcome Assessment

Focal Temperature

Focal temperature (Tmax) is defined as the average temperature on a 3 × 3 grid with a target in the center. Previous clinical evidence has suggested that a peak temperature of 54°C–60°C was sufficient to cause lesioning with a higher safety profile.[9] We divided Tmax into two groups: Tmax ≤ 54°C and Tmax > 54°C. While sonications with a peak temperature above 54°C have been reported to result in tissue ablation, sonications at lower temperatures (50°C–54°C) have also been shown to contribute to lesion formation.[10,11] The low-temperature (50°C–54°C)[10] group was analyzed using temperature thresholds of 50°C, 52°C, and 54°C based on the suggested number of sonications at 52°C and 54°C that significantly correlated with lesion volumes in the literature.[12]

Tremor

Clinical evaluation was performed using the Clinical Rating Scale for Tremor (CRST) scores, as detailed by Stacy et al.[13] The upper extremity tremor subscore (CRST subscore) for the treated hand was calculated by summing the observed and performance-based scores from CRST parts A and B.[14] A movement disorder specialist at each center evaluated tremors at baseline and at 1, 3, 6, and 12 months posttreatment to determine the severity of symptoms and the degree of functional impairment. In this study, efficacy was defined as a reduction in tremor at 12 months posttreatment with clinical symptom relief. Patients in the current study were divided into two groups based on the CRST subscore (< 10 or ≥ 10) at the 12-month follow-up, referring to the randomized controlled trial in which the mean score for hand tremor improved by 47% (9.6 ± 5.1) in the thalamotomy group.[5]

Adverse Events

All adverse events were classified as mild, moderate, or severe on the basis of the maximal severity of the event at any time:[15] a mild adverse event was defined as a minor inconvenience that did not affect routine daily activities, a moderate adverse event was defined as a bothersome event that interfered with routine daily activities, and a severe adverse event was defined as an incapacitating event that prevented activities of daily living. Thalamotomy-related adverse events (T-AEs) were categorized into four groups for analysis: sensory, speech and swallowing, balance and gait, and weakness abnormalities.[15] Safety was based on the incidence of reported T-AEs.

Statistical Analysis

Statistical analyses were performed using SAS (version 9.4, SAS Inc.). For related categories, comparisons were made using unpaired sample t-tests and chi-square tests for continuous variables and categorical variables, respectively, and $p < 0.05$ was considered statistically significant. For evaluating improvement based on a comparison of CRST scores over time, a one-way repeated-measures

ANOVA was performed. Correlations between potential influencing parameters (patient-related factors and sonication parameters) and improvement in the CRST scores were calculated using linear regression and logistic regression methods.

Results

Patient Demographics and Treatment-Related Parameters

During the follow-up period, 10 patients were excluded because of loss to follow-up or insufficient data. The data for 250 patients who had entered the open-label phase of the study and had been monitored for 12 months were considered valid. The mean age of the patients was 69.4 ± 11.0 years (range 26–92 years). One hundred seventy-two patients were male (68.8%) and 78 were female (31.2%). There were slightly more White patients than Asian patients (131 vs 109), and there were only 10 Black or Hispanic patients. The patients' mean SDR, skull volume, and incidence angle were 0.50 ± 0.11, 237.5 ± 55.1 cm^3, and 13.1° ± 1.1°, respectively. The mean number of active transducer elements and the corresponding skull area were 903.8 ± 49.6 and 334.2 ± 38.6 cm^2, respectively. With the implementation of multiple focused ultrasound sonications (15.7 ± 5.2), a mean Tmax of 56.3°C ± 2.6°C was achieved using a maximal energy of 17,527.4 ± 9063.5 J. The mean maximal power and duration of sonication were 852.0 ± 211.2 W and 23.1 ± 8.9 seconds, respectively (Table 1).

TABLE 1. Demographic characteristics and treatment-related parameters

Variable	Value
Age in yrs (range)	69.4 ± 11.0 (26–92)
Sex, no. (%)	
M	172 (68.8%)
F	78 (31.2%)
Race, no. (%)	
White	131 (52.4%)
Asian	109 (43.6%)
Black or Hispanic	10 (4%)
SDR (range)	0.50 ± 0.11 (0.27–0.82)
Skull vol in cm^3 (range)	237.5 ± 55.1 (107.44–406.57)
Incidence angle in ° (range)	13.1 ± 1.1 (10.15–16.05)
No. of active transducer elements (range)	903.8 ± 49.6 (699.63–1,017.92)
Skull area in cm^2 (range)	334.2 ± 38.6 (14.56–413.5)
Max energy in J (range)	17,527.4 ± 9,063.5 (3,351.4–44,288)
Max power in W (range)	852.0 ± 211.2 (350–1,297.09)
Max duration in sec (range)	23.1 ± 8.9 (9–46)
Tmax in °C (range)	56.3 ± 2.6 (39.91–63.87)
No. of sonications (range)	15.7 ± 5.2 (6–35)
CRST subscore at baseline	18.7 ± 5.2 (4–32)

Descriptive statistics are presented as the mean ± standard deviation.

Tremor Improvement and Potential Related Factors

The mean baseline CRST subscore among all patients was 18.7 ± 5.2. The patients' tremors improved by 67.8% ± 26.2%, 64.4% ± 26.3%, 63.4% ± 26.1%, and 61.5% ± 26.3% at 1, 3, 6, and 12 months posttreatment, respectively (Fig. 1A). Improvement was sustained throughout the 12-month follow-up, and 184 (73.6%) of the 250 patients had minimal or no disability due to tremor (CRST subscore < 10) at the 12-month follow-up. In the logistic regression analysis of CRST subscore < 10 at the 1-year follow-up and its relationship with patient demographics and treatment-related parameters (Table 2), we found that younger age, fewer sonications, fewer cavitation halts, and lower baseline CRST subscore significantly correlated with a CRST subscore < 10. More active transducer elements, larger skull areas, and higher Tmax were positively correlated with a CRST subscore < 10. In the multivariate analysis, younger age and higher Tmax were significantly related to tremor outcome (OR 0.948 and p = 0.013, OR 1.188 and p = 0.025, respectively). Based on the data available, the SDR and accumulated thermal dose showed no significant relationships with tremor improvement (p = 0.869 and = 0.832, respectively).

Tmax

As shown in Fig. 1B, tremor improvement tended to increase as Tmax increased. Since there were few cases involving the upper and lower limits of the temperature range, data points were averaged with their neighboring cases. The mean improvement in CRST scores for treatments with 50°C ≤ Tmax ≤ 52°C (n = 11; another case involving Tmax of 40°C was excluded from Fig. 1B) was 35.6% ± 29.2%. For treatments with Tmax ≥ 61°C (n = 9), the mean improvement was 60.0% ± 25.7%.

The improvements in CRST scores for patients with Tmax ≤ 54°C were significantly lower than those for patients with Tmax > 54°C at all follow-up points: 55.1% ± 32.7% versus 71.4% ± 23.0% at 1 month, 52.1% ± 30.9% versus 67.9% ± 23.3% at 3 months, 54.1% ± 29.3% versus 66.0% ± 24.0% at 6 months, and 49.9% ± 27.5% versus 64.7% ± 25.1% at 12 months after treatment (p < 0.01; Fig. 1A). Asian patients had a significantly lower SDR than White patients (0.46 ± 0.11 vs 0.53 ± 0.10, p < 0.0001), and the Tmax achieved in Asian patients was lower (55.8°C ± 2.5°C vs 56.8°C ± 2.7°C, p = 0.003). However, there were no significant differences in tremor improvement between Asian and White patients (64.1% ± 28.6% vs 59.0% ± 24.2%, p = 0.142; Fig. 1A).

Linear regression indicated that Tmax positively correlated with SDR, active elements, skull area, and accumulated thermal dose and negatively correlated with race (lower value in Asian patients), maximal energy, maximal power, maximal duration, and cavitation halts (Table 3). The multivariate analysis revealed no single statistically significant factor correlated with Tmax. The cutoff for a Tmax predicting a CRST subscore < 10 was 55.8°C according to our calculation of the maximal area under the receiver operating characteristic curve (Fig. 1C).

Repetition and Number of Sonications

Analysis of the low-temperature group indicated that

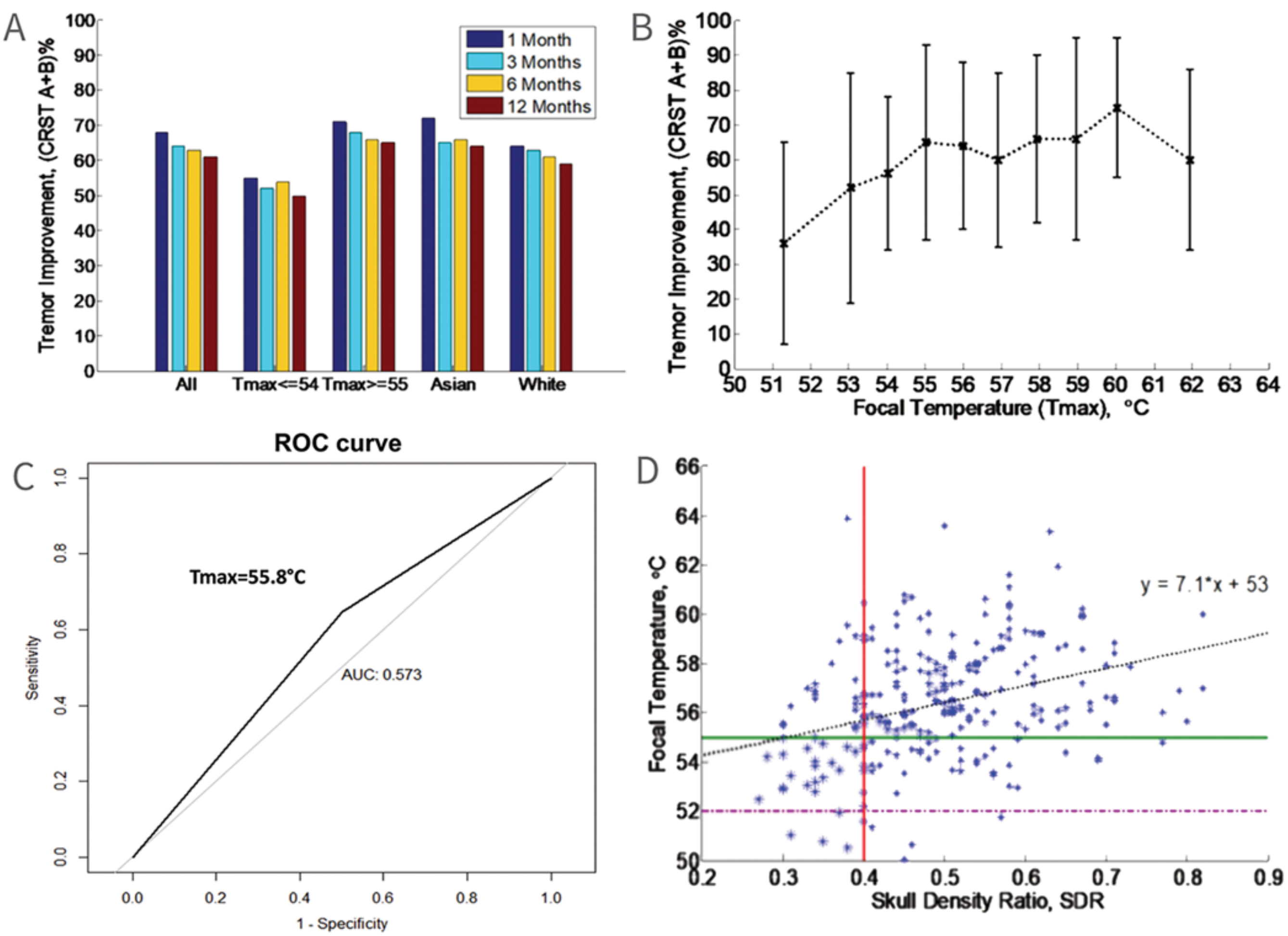

FIG. 1. A: Tremor improvements during the 12-month follow-up: all patients valid for analysis (n = 250), patients with Tmax ≤ 54°C (n = 55), patients with Tmax > 54°C (n = 195), Asian patients (n = 109), and White patients (n = 131). **B:** Relationship between tremor improvement at the 12-month follow-up (percentage change in CRST subscore) and Tmax. **C:** Receiver operating characteristic (ROC) curve of Tmax to predict a CRST subscore < 10. Area under the receiver operating characteristic curve (AUC) = 0.573, cutoff value for Tmax = 55.8°C. **D:** SDR according to the Tmax achieved. *Horizontal lines* indicate temperature thresholds of 52°C (*magenta*) and 55°C (*green*), and the *red vertical line* indicates an SDR of 0.4. Figure is available in color online only.

Tmax and the number of repetitions with a Tmax ≥ 52°C showed a positive relationship with tremor control ($p = 0.002$; Table 4). A significant difference in tremor improvement was noted between treatments with ≤ 2 sonications with a Tmax reaching 52°C and those with ≥ 3 sonications with a Tmax reaching 52°C (30.8% ± 29.3% vs 58.5% ± 22.2%, $p < 0.0001$; Table 5). Considering the number of targets, it was feasible to deliver 1–3 sonications per right target with a Tmax between 52°C and 54°C for effective tremor suppression (58.0% ± 22.2% [n = 32] vs 38.7% ± 30.6% [n = 23] when the number of repetitions per target was < 1, $p < 0.01$). In the high-temperature group, Tmax and the number of sonications exhibited no significant relationship with tremor improvements ($p = 0.444$). No significant benefits of repeating sonications at higher temperatures were noted, while the number of sonications with Tmax ≥ 50°C showed an inverse relationship with tremor improvement ($p = 0.002$; Table 4).

Skull Properties and Heating Outcomes

The linear regression analysis between various skull properties and heating efficiency indicated that SDR was positively correlated with heating efficiency (i.e., $\delta T/\delta E$, where δT represents the temperature achieved minus a baseline temperature of 37°C and δE represents the energy delivered at the maximum temperature; $\beta = 0.005$ and $p < 0.001$), while skull volume and incidence angle were negatively correlated ($\beta = -3E06$ and $p < 0.001$, $\beta = -0.0001$ and $p < 0.014$, respectively). Multivariate analysis was not performed because of multicollinearity. Among the 250 patients, 43 had an SDR < 0.4, 40 of whom (93.0%) had a Tmax ≥ 52°C, and 24 of whom (55.8%) had a Tmax ≥ 55°C (Fig. 1D).

Safety Outcomes

T-AEs were usually mild (85.7% and 86.7% in the low- and high-temperature groups, respectively) and rarely

TABLE 2. CRST subscore < 10 at the 1-year follow-up and related factors: logistic regression

	Univariate		Multivariate	
Variable	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	0.929 (0.897–0.963)	**<0.001**	0.948 (0.909–0.989)	**0.013**
Sex	0.663 (0.367–1.198)	0.174		
Race				
Asian (vs White)	1.557 (0.866–2.797)	0.139		
Other (vs White)	1.758 (0.357–8.648)	0.488		
SDR	1.237 (0.100–15.357)	0.869		
Skull vol	1.000 (0.995–1.005)	0.982		
Incidence angle	0.877 (0.675–1.140)	0.327		
No. of active elements	1.011 (1.005–1.017)	**<0.001**	1.007 (0.998–1.015)	0.120
Skull area	1.013 (1.004–1.022)	**0.003**	1.001 (0.991–1.012)	0.774
Max energy	1.000 (1.000–1.000)	0.881		
Max power	1.000 (0.999–1.002)	0.568		
Max duration	0.992 (0.962–1.024)	0.631		
Tmax	1.152 (1.028–1.290)	**0.015**	1.188 (1.022–1.380)	**0.025**
No. of sonications	0.918 (0.869–0.969)	**0.002**	0.954 (0.886–1.026)	0.203
Cavitation halts	0.807 (0.672–0.969)	**0.022**	0.949 (0.732–1.231)	0.694
Patient stops	0.835 (0.675–1.032)	0.096		
Thermal dose	1.390 (0.066–29.119)	0.832		
CRST subscore at baseline	0.789 (0.734–0.848)	**<0.001**	0.795 (0.732–0.863)	<0.001

Boldface type indicates statistical significance ($p < 0.05$).

TABLE 3. Tmax and related factors: linear regression

	Univariate		Multivariate	
Variable	β (SE)	p Value	β (SE)	p Value
Age	0.005 (0.015)	0.7374		
Sex	−0.366 (0.357)	0.3067		
Race				
Asian (vs White)	−0.980 (0.335)	**0.004**	−0.581 (0.347)	0.095
Other (vs White)	−0.186 (0.848)	0.826	−0.998 (0.719)	0.167
SDR	7.069 (1.414)	**<0.001**	3.484 (1.589)	0.029
Skull vol	−0.005 (0.003)	0.080		
Incidence angle	−0.279 (0.155)	0.073		
Active elements	0.010 (0.003)	**0.0032**	0.013 (0.004)	<0.001
Skull area	0.013 (0.004)	**0.003**	0.007 (0.004)	0.099
Max energy	−1E−04 (2E−05)	**<0.001**	−5E−05 (3E−05)	0.131
Max power	−0.003 (8E−04)	**<0.001**	−0.015 (9E−04)	0.241
Max duration	−0.116 (0.017)	**<0.001**	−0.060 (0.036)	0.099
No. of sonications	−0.035 (0.032)	0.273		
Cavitation halts	−0.385 (0.116)	**0.001**	−0.087 (0.108)	0.423
Patient stops	−0.367 (0.133)	0.006		
Thermal dose	8.098 (1.675)	**<0.001**	10.320 (1.487)	<0.001
CRST subscore at baseline	−0.016 (0.032)	0.607		

SE = standard error.
Boldface type indicates statistical significance ($p < 0.05$).

TABLE 4. Repetitions and their correlations with clinical improvement

Repetitions	Tmax ≤54°C (n = 55) Mean ± SD	p Value	r	Tmax >54°C (n = 195) Mean ± SD	p Value	r
Repetitions (Tmax 50°C)	6.0 ± 2.6	0.112	0.219	7.7 ± 3.2	**0.002**	−0.224
Repetitions (Tmax ≥52°C)	3.4 ± 2.2	**0.002**	0.408	5.8 ± 2.5	**0.045**	−0.144
Repetitions (Tmax 54°C)	1.0 ± 1.2	0.071	0.248	3.6 ± 2.0	0.084	−0.124
Repetitions (Tmax ≥57°C)	NA	NA	NA	1.1 ± 1.1	0.498	−0.049

NA = not applicable.
Boldface type indicates statistical significance ($p < 0.05$).

severe (0% and 2.2% in the low- and high-temperature groups, respectively). Balance (47.1%) and sensory (34.7%) abnormalities were the most commonly reported T-AEs. The high-temperature group had a higher rate of balance disturbances ($p = 0.04$; Table 6).

Discussion

In this study, we retrospectively reviewed a large cohort of patients who had undergone unilateral MRgFUS thalamotomy for ET. We aimed to develop best practices in the growing field of ultrasound lesioning. A hand-specific CRST subscore was used to compare results for the treated hand. We evaluated the potentially related factors that may assist in improving the clinical outcomes of MRgFUS thalamotomy on the basis of an analysis of 250 patients. We found that younger age and higher Tmax correlated with tremor improvement in the multivariate analysis. SDR, active elements, skull area, and thermal dose positively correlated with Tmax, and maximal energy, maximal power, maximal duration, and cavitation halts negatively correlated with Tmax in the univariate analysis. However, no statistically significant factor correlated with Tmax in the multivariate analysis.

Tmax and Repetitions

The study demonstrated that improvements in the CRST subscore overall increased as Tmax increased (Fig. 1B). Although there is still no agreement on what temperature threshold is necessary to cause permanent tissue necrosis, previous clinical evidence has shown that a peak temperature of 54°C–60°C is sufficient to complete lesioning.[16–18] In the current study, we calculated a Tmax cutoff value of 55.8°C to achieve a CRST subscore < 10 at the 12-month follow-up (Fig. 1C). Since Tmax was the statistically significant factor for a CRST subscore < 10 at the 12-month follow-up (Table 2), Tmax is crucial for successful treatment. While sonication with peak temperatures > 55°C has been reported to cause tissue ablation in a few seconds,[19,20] sonications at lower temperatures (50°C–54°C) have also been shown to contribute to lesion formation.[10–12] It has been reported that repeated low-temperature (50°C–54°C) sonications can accumulate a sufficient thermal dose to generate lesions for clinically relevant tremor suppression up to 1 year posttreatment.[10] In the present cases involving 52°C ≤ Tmax ≤ 54°C, 1–3 repetitions at the right target seemed sufficient for tremor improvement (Table 5). Modulating the duration of sonications is also required when Tmax is limited to below 54°C. In a previous study, we suggested that 1 second at 57°C was sufficient for tissue necrosis, whereas tissue necrosis with a Tmax of 54°C required 7 seconds.[11] In the high-temperature group, Tmax and number of sonications exhibited no significant relationship with tremor improvements (Table 4). When the target is correct, repetitions seem less necessary for the amelioration of tremor. Since there was no single statistically significant factor for Tmax in the multivariate analysis (Table 3), proper modification of treatment parameters should be performed for patients in whom it is difficult to reach a target temperature of 54°C in order to overcome the fact that SDR was positively correlated with Tmax in the univariate analysis.

Skull Properties for Patient Screening

SDR, defined as the ratio between the densities of marrow and cortical bone, has been identified as the dominant indicator of ultrasound energy transmission through the skull.[11] According to the Food and Drug Administration, patients with an SDR of 0.45 ± 0.05 or more, as calculated by screening CT, are eligible for treatment. With additional experience and a greater accumulation of knowledge worldwide, researchers have found that patient-specific information such as the skull volume in the treatment area and the incidence angle of the ultrasound beam against the skull surface are also associated with poor heating.[21] The SDR criterion has been adjusted to 0.30 ± 0.05 in the continued-access study at new centers in Asia. Based on

TABLE 5. Low-temperature group: repetitions at Tmax ≥ 52°C

Variable	No. of Patients	Sonications at 52°C ≤ Tmax ≤ 54°C	No. of Targets	Repetitions (52°C) per Target	Tremor Improvement
Repetitions (52°C) ≤2	17	0.82 ± 0.81	1.94 ± 0.83	0.39 ± 0.41	30.8% ± 29.3%
Repetitions (52°C) ≥3	38	4.42 ± 1.65	3.34 ± 2.17	1.90 ± 1.55	58.5% ± 22.2%
Total	55	3.31 ± 2.21	2.91 ± 1.97	1.43 ± 1.48	49.9% ± 27.5%

TABLE 6. T-AEs by severity and type

Event Category	Tmax ≤54°C (n = 55)			Tmax >54°C (n = 195)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Balance	16	3	0	88	17	5
Sensory	17	3	0	71	4	0
Strength	5	0	0	18	4	0
Speech	4	1	0	18	0	0

the present analysis, SDR had no significant correlation with tremor outcome (Table 2). This finding is consistent with previous literature suggesting that there is no significant association between tremor outcomes and SDR, although SDR is still important for assessing technical eligibility for successful MRgFUS thalamotomies.[22–25] In the present study, we found that SDR was positively correlated with heating efficiency (i.e., $\delta T/\delta E$ at the maximum temperature; $\beta = 0.005$, $p < 0.001$). Previous results from both ex vivo and in vivo skulls have indicated that a high SDR is more efficient at energy transmission and at raising temperatures to make permanent lesions in the brain.[21] Moreover, it has been reported that the amount of required energy varies in patients with a low SDR and that it is difficult to predict the temperature rise.[24] We assumed that the reason there was no correlation between SDR and CRST improvement was because 55.8°C (the lower cutoff value of Tmax) was a high enough temperature for a successful clinical outcome, although higher energy (power and duration) was required to achieve the desired ablative temperature. Once treatment parameters are modulated to deliver enough energy, SDR itself may be correlated with Tmax but not with clinical outcomes. The present study suggests that lowering the cutoff value of SDR may be possible in patients who are able to withstand pain caused by high energy transmission and prolonged treatment. Thus, in the case of low SDR, younger patients are recommended as candidates for MRgFUS. Increased power and longer durations are required when treating Asian patients, who have a significantly lower SDR than White patients (0.46 ± 0.11 vs 0.53 ± 0.10, $p < 0.0001$). Furthermore, higher energy during sonication requires a longer cooling time after each sonication. Dynamic processes in the brain tissue during these intervals may affect tissue response, causing the appearance of cavitations in the tissue.[26] Advanced MRgFUS technology to prevent abnormal cavitation signals could enable us to overcome issues associated with low SDR.

Number of Sonications

Chang et al. mentioned that in their series, to achieve the desired clinical effect, patients had 2–7 suprathreshold sonications (10 seconds each) and a total of 15–28 sonications (including subthreshold).[27] In the current analysis, a higher number of sonications showed an inverse correlation with a CRST subscore < 10 in the univariate logistic regression (Table 2). Previous studies have also suggested that a higher number of sonications is associated with poor outcomes, which may be related to the use of high acoustic power requiring a high number of sonications.[23,28] However, it should not be considered as the causative factor for treatment success. The number of sonications in each treatment can be affected by the efficiency of ultrasound energy transmission through the skull, the process of target alignment (to calibrate the targeting accuracy in each orthogonal plane), energy titration strategies with respect to a therapeutic dose, and relocation of the target based on patient feedback. Considering the complexities and challenges presented during treatment, we found that the number of sonications showed an inverse correlation with tremor suppression. $\delta T/\delta E$ (°C/J) represents temperature achieved minus a baseline temperature of 37°C divided by energy delivered. A larger value of dT/dE means that a greater change in temperature can be raised with the same amount of energy. Bond and Elias observed an increase in the energy requirement for each subsequent treatment sonication, with the largest percentage increase from the first sonication treatment to the second.[29] In practice, for patients with a low SDR, heating efficiency decreases dramatically during the treatment process while the number of sonications increases,[28,29] which means energy is not used effectively to increase temperature. Thus, it may help to achieve a therapeutic temperature with a significant increase of energy once the alignment is completed. In particular, when treating patients with low SDRs, we suggest increasing the temperature to the therapeutic range with delivered energy early in the treatment, before the change in skull properties and brain tissues causes the appearance of cavitations. Furthermore, if the physician fails to achieve an ablative temperature after a certain number of sonications at any single target, it would be beneficial to move the target slightly within the safety zone based on the patient's response.

Adverse Events

The goal of MRgFUS thalamotomy in patients with ET is to ablate the VIM until the tremor is suppressed to a satisfactory level. The clinical efficacy of MRgFUS is important, but its safety must also be considered. Despite the promising efficacy demonstrated in a previous randomized controlled study by Elias et al.,[5] the treatment was associated with a nonnegligible rate of adverse events, which eventually decreased by the 12-month follow-up. Both 2-year[6] and 4-year[8] follow-up studies showed clinical efficacy and an acceptable range of adverse events. Inaccurate targeting of the VIM and/or the development of perilesional edema can affect other thalamic nuclei and adjacent structures, such as the posterior limb of the internal capsule.[30,31] In the current analysis, T-AEs were usually mild, and balance and sensory abnormalities were the most commonly reported. The high-temperature group (Tmax > 54°C) had a higher incidence of balance disturbances than the low-temperature group ($p = 0.04$). Higher temperatures are expected to generate longer-lasting results but may also lead to a higher rate of side effects;[32] therefore, lesioning procedures require a balance between efficacy and safety. Furthermore, lesioning procedures require a balance between lesion size and the risk of adverse effects, since larger lesions are expected to result in longer-lasting efficacy but also a higher incidence of side effects.[5,12,14] Although the current study did not investigate volumetric analysis, researchers have tried to link the location and size of thermal lesions with tremor reduction and adverse effects.[12,14,29,30,33,34] Even with a low Tmax, the accumulated thermal dose has been demonstrated to influence lesion size, which has been shown to be correlated with the incidence of adverse effects.[10,35]

Study Limitations

This retrospective analysis of prospectively collected data has several limitations. 1) The continued-access trial is the same as the clinical study by Elias et al.[5] but with no sham data available for comparison. 2) Efficacy and safety were evaluated by neurologists who specialize in movement disorders at different institutions, which might have generated subjective and biased results among institutions. 3) The physician's experience with functional surgery and the learning curve for MRgFUS thalamotomy could have affected the treatment outcomes. 4) Treatment strategies, such as targeting (indirect targeting based on atlas-derived coordinates or with the incorporation of tractography), utilization of power, duration, and energy, varied from institution to institution. We did not analyze the data regarding target movements, which may have differed between centers and affected the clinical outcomes. 5) The CT imaging protocols varied across different vendors and models. Standardized guidelines for CT scanning will be needed to make general comparisons. 6) We only evaluated parts A and B of the CRST and did not investigate part C. Jung et al. found that the score for CRST part C showed a 55.1% improvement from baseline to the 12-month follow-up. Furthermore, the total score for the Quality of Life in Essential Tremor Questionnaire also showed the same trend of improvement.[36] However, further investigations in terms of functional disability and quality of life are needed. 7) The present analysis focused on technical and operative variables, which are important in clinical practice. Our study did not include volumetric analysis after MRgFUS thalamotomy. Thus, we could not examine the relationship between lesion volume and tremor improvement according to sonication parameters. Follow-up studies identifying the topography and size of lesions that caused adverse events are necessary. 8) All adverse events were classified as mild, moderate, or severe on the basis of maximal severity. A more objective and quantifiable classification system for adverse events is needed because the physicians classified the adverse events at their discretion, which could have resulted in subjective and biased results. 9) Finally, a longer follow-up is necessary to confirm our conclusions.

Conclusions

In this study, we summarized and presented data from 250 patients who had undergone unilateral MRgFUS thalamotomy for ET and completed 12 months of follow-up. Our data may help to improve overall clinical outcomes and minimize adverse events in the clinical setting. This analysis of a large cohort of ET patients may provide a better understanding of MRgFUS thalamotomy practices and further improve the safety, efficacy, and efficiency of this treatment. However, further investigations and continuous follow-ups are necessary to confirm our conclusions.

Acknowledgments

This work was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HI19C0060).

References

1. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? estimates of the prevalence of essential tremor throughout the world. *Mov Disord*. 1998;13(1):5–10.
2. Zappia M, Albanese A, Bruno E, et al. Treatment of essential tremor: a systematic review of evidence and recommendations from the Italian Movement Disorders Association. *J Neurol*. 2013;260(3):714–740.
3. Flora ED, Perera CL, Cameron AL, Maddern GJ. Deep brain stimulation for essential tremor: a systematic review. *Mov Disord*. 2010;25(11):1550–1559.
4. Higuchi Y, Matsuda S, Serizawa T. Gamma knife radiosurgery in movement disorders: Indications and limitations. *Mov Disord*. 2017;32(1):28–35.
5. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med*. 2016;375(8):730–739.
6. Chang JW, Park CK, Lipsman N, et al. A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: results at the 2-year follow-up. *Ann Neurol*. 2018;83(1):107–114.
7. Halpern CH, Santini V, Lipsman N, et al. Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. *Neurology*. 2019;93(24):e2284–e2293.
8. Park YS, Jung NY, Na YC, Chang JW. Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Mov Disord*. 2019;34(5):727–734.
9. Jung NY, Park CK, Kim M, et al. The efficacy and limits of magnetic resonance-guided focused ultrasound pallidotomy for Parkinson's disease: a Phase I clinical trial. *J Neurosurg*. 2019;130(6):1853–1861.
10. Jones RM, Kamps S, Huang Y, et al. Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: repeated sonications with low focal temperatures. *J Neurosurg*. 2020;132(6):1802–1809.
11. Chang WS, Jung HH, Zadicario E, et al. Factors associated with successful magnetic resonance-guided focused ultrasound treatment: efficiency of acoustic energy delivery through the skull. *J Neurosurg*. 2016;124(2):411–416.
12. Pineda-Pardo JA, Urso D, Martínez-Fernández R, et al. Transcranial magnetic resonance-guided focused ultrasound thalamotomy in essential tremor: a comprehensive lesion characterization. *Neurosurgery*. 2020;87(2):256–265.
13. Stacy MA, Elble RJ, Ondo WG, et al. Assessment of interrater and intrarater reliability of the Fahn-Tolosa-Marin Tremor Rating Scale in essential tremor. *Mov Disord*. 2007;22(6):833–838.
14. Federau C, Goubran M, Rosenberg J, et al. Transcranial MRI-guided high-intensity focused ultrasound for treatment of essential tremor: a pilot study on the correlation between lesion size, lesion location, thermal dose, and clinical outcome. *J Magn Reson Imaging*. 2018;48(1):58–65.
15. Fishman PS, Elias WJ, Ghanouni P, et al. Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. *Mov Disord*. 2018;33(5):843–847.
16. Vykhodtseva N, Sorrentino V, Jolesz FA, et al. MRI detection of the thermal effects of focused ultrasound on the brain. *Ultrasound Med Biol*. 2000;26(5):871–880.
17. Magara A, Bühler R, Moser D, et al. First experience with

MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound*. 2014;2:11.

18. Jeanmonod D, Werner B, Morel A, et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. *Neurosurg Focus*. 2012;32(1):E1.
19. McDannold N, King RL, Hynynen K. MRI monitoring of heating produced by ultrasound absorption in the skull: in vivo study in pigs. *Magn Reson Med*. 2004;51(5):1061–1065.
20. Elias WJ, Khaled M, Hilliard JD, et al. A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus. *J Neurosurg*. 2013;119(2): 307–317.
21. Jung NY, Rachmilevitch I, Sibiger O, et al. Factors related to successful energy transmission of focused ultrasound through a skull: a study in human cadavers and its comparison with clinical experiences. *J Korean Neurosurg Soc*. 2019; 62(6):712–722.
22. Chang KW, Park YS, Chang JW. Skull factors affecting outcomes of magnetic resonance-guided focused ultrasound for patients with essential tremor. *Yonsei Med J*. 2019;60(8): 768–773.
23. Krishna V, Sammartino F, Cosgrove R, et al. Predictors of outcomes after focused ultrasound thalamotomy. *Neurosurgery*. 2020;87(2):229–237.
24. Boutet A, Gwun D, Gramer R, et al. The relevance of skull density ratio in selecting candidates for transcranial MR-guided focused ultrasound. *J Neurosurg*. 2020;132(6):1785–1791.
25. D'Souza M, Chen KS, Rosenberg J, et al. Impact of skull density ratio on efficacy and safety of magnetic resonance-guided focused ultrasound treatment of essential tremor. *J Neurosurg*. 2020;132(5):1392–1397.
26. Sinai A, Nassar M, Eran A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience. *J Neurosurg*. 2020;133(2):417–424.
27. Chang WS, Jung HH, Kweon EJ, et al. Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. *J Neurol Neurosurg Psychiatry*. 2015;86(3):257–264.
28. Hughes A, Huang Y, Schwartz ML, Hynynen K. The reduction in treatment efficiency at high acoustic powers during MR-guided transcranial focused ultrasound thalamotomy for essential tremor. *Med Phys*. 2018;45(7):2925–2936.
29. Bond AE, Elias WJ. Predicting lesion size during focused ultrasound thalamotomy: a review of 63 lesions over 3 clinical trials. *Neurosurg Focus*. 2018;44(2):E5.
30. Boutet A, Ranjan M, Zhong J, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. *Brain*. 2018;141(12):3405–3414.
31. Gross RE, Krack P, Rodriguez-Oroz MC, et al. Electrophysiological mapping for the implantation of deep brain stimulators for Parkinson's disease and tremor. *Mov Disord*. 2006; 21(suppl 14):S259–S283.
32. Schuurman PR, Bosch DA, Merkus MP, Speelman JD. Long-term follow-up of thalamic stimulation versus thalamotomy for tremor suppression. *Mov Disord*. 2008;23(8):1146–1153.
33. Wintermark M, Druzgal J, Huss DS, et al. Imaging findings in MR imaging-guided focused ultrasound treatment for patients with essential tremor. *AJNR Am J Neuroradiol*. 2014; 35(5):891–896.
34. Fukutome K, Kuga Y, Ohnishi H, et al. What factors impact the clinical outcome of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor? *J Neurosurg*. 2021;134(5):1618–1623.
35. Huang Y, Lipsman N, Schwartz ML, et al. Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. *Med Phys*. 2018;45(10):4704–4710.
36. Jung NY, Park CK, Chang WS, et al. Effects on cognition and quality of life with unilateral magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. *Neurosurg Focus*. 2018;44(2):E8.

Disclosures

Dr. J. W. Chang reports receiving grant support from InSightec (Haifa, Israel) for clinical trials related to MRgFUS treatment of essential tremor and Parkinson disease.

Author Contributions

Conception and design: JW Chang, Rachmilevitch. Acquisition of data: Y Kim, Gao, Kovalevsky, Rachmilevitch. Analysis and interpretation of data: MJ Kim, Y Kim. Drafting the article: MJ Kim. Critically revising the article: WS Chang, Jung. Reviewed submitted version of manuscript: WS Chang, Jung. Approved the final version of the manuscript on behalf of all authors: JW Chang. Statistical analysis: MJ Kim, Park, Gao. Administrative/technical/material support: KW Chang, Gao, Kovalevsky, Rachmilevitch. Study supervision: JW Chang, Zadicario.

Correspondence

Jin Woo Chang: Yonsei University College of Medicine, Seoul, Republic of Korea. jchang@yuhs.ac.